



RECEIVED

SEP 19 2000

TECH CENTER 1600/2500 PATENT ATTORNEY DOCKET NO. 50010/006006

Certificate of Mailing: Date of Deposit: September 8, 2000

I hereby certify under 37 CFR 1.8(a) that this correspondence is being deposited with the United States Postal Service as **first class mail** with sufficient postage on the date indicated above and is addressed to the Director for Patents, Washington, D.C. 20231.

Nicky McKinnon

*Nicky McKinnon*

Printed name of person mailing correspondence

Signature of person mailing correspondence

#3  
S.G.J.  
9/20/00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Douglas A. Treco *et al.*

Art Unit: Not Yet Assigned

Serial No.: 09/431,821

Examiner: Not Yet Assigned

Filed: November 2, 1999

Title: Targeted Introduction of DNA into Primary or Secondary Cells and Their Use for Gene Therapy and Protein Production

Director for Patents  
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Applicants submit the references listed on the enclosed form PTO 1449.

Submission of this statement is not a representation that a search has been made, nor is information included in this statement an admission that the information is material to patentability.

RECEIVED

SEP 19 2003

TECH CENTER 1600/2900

Under 35 U.S.C. § 120, this application relies on the earlier filing date of application serial number 08/446,928, filed on May 18, 1995. The following references were submitted to and/or cited by the Office in the prior application and, therefore, are not provided in this application:

4,396,601	2 Aug 1983	Salser <i>et al.</i>
4,497,796	2 May 1985	Salser <i>et al.</i>
4,703,008	27 Oct 1987	Lin
4,789,550	12 Jun 1988	Hommel <i>et al.</i>
4,892,538	1 Sep 1990	Aebischer <i>et al.</i>
4,980,286	25 Dec 1990	Morgan <i>et al.</i>
5,082,670	21 Jan 1992	Gage <i>et al.</i>
5,089,397	18 Feb 1992	Kushner <i>et al.</i>
5,166,059	24 Nov 1992	Pastan <i>et al.</i>
5,175,255	29 Dec 1992	Thomason <i>et al.</i>
5,194,596	14 Dec 1989	Tischer <i>et al.</i>
5,219,740	15 Jun 1993	Miller <i>et al.</i>
5,272,071	21 Dec 1993	Chappel
5,399,346	21 Mar 1995	Anderson <i>et al.</i>
5,460,959	24 Oct 1995	Mulligan <i>et al.</i>
5,464,764	7 Nov 1995	Capecchi <i>et al.</i>
5,578,461	26 Nov 1996	Sherwin <i>et al.</i>
5,789,215	4 Aug 1998	Berns <i>et al.</i>
WO 87/00201	15 Jan 1987	PCT
WO 88/00239	14 Jan 1988	PCT
WO 88/08306	03 Mar 1988	PCT
WO 89/01517	23 Feb 1989	PCT

WO 89/05345	11 Dec 1987	PCT
WO 89/07136	05 Feb 1988	PCT
WO 90/06757	28 Jun 1990	PCT
WO 90/06997	13 Dec 1988	PCT
WO 90/11354	04 Oct 90	PCT
WO 90/12878	22 May 1989	PCT
WO 90/15863	13 Jun 1989	PCT
WO 91/06666	16 May 1991	PCT
WO 91/06667	16 May 1991	PCT
WO 91/09955	11 Jul 1991	PCT
WO 91/13151	05 Sep 1991	PCT
WO 91/19796	26 Dec 1991	PCT
WO 92/03917	19 Mar 1992	PCT
WO 92/07573	31 Oct 1990	PCT
WO 92/08796	29 Mar 1992	PCT
WO 92/12242	26 Dec 1990	PCT
WO 92/15676	08 Mar 1991	PCT
WO 92/19255	12 Nov 1992	PCT
WO 92/20808	26 Nov 1992	PCT
WO 93/04169	04 Mar 1993	PCT
EP 0038765	22 Mar 1981	Europe
EP 0236059	09 Sep 1987	Europe
EP 0255231	03 Feb 1988	Europe
EP 0289034	02 Nov 88	Europe
EP 0452894	23 Oct 1991	Europe
EP Opposition	30 Apr 98	On behalf of Genetic Therapy, Inc.
EP Opposition	30 Apr 98	On behalf of Institut Pasteur

RECEIVED

21 19 2003

TECH CENTER 1600/2800

EP Opposition	04 May 98	On behalf of Boehringer Mannheim GMBH
EP Opposition	04 May 98	On behalf of Applied Research Systems
EP Opposition	04 May 98	On behalf of Cell Genesys, Inc.
2159172	27 Nov 1985	Great Britain

RECEIVED  
SEP 19 2003  
TECH CENTER 1600/2000

Alberts, *Molecular Biology of the Cell (Glossary)*, third edition, Garland Publishing, Inc., New York.

Antin *et al.*, "Single Cell Analysis of Transfected Gene Expression in Primary Heart Cultures Containing Multiple Cell Types," *BioTechniques* 6:640-648, 1988.

Barr *et al.*, "Systemic Delivery of Recombinant Proteins by Genetically Modified Myoblasts," *Science*, 254:1507-1509, 1991.

Behr *et al.*, "Efficient Gene Transfer Into Mammalian Primary Endocrine Cells with Lipopolyamine-coated DNA," *Proceedings of the National Academy of Sciences U.S.A.* 86:6982-6986, 1989.

Bennett *et al.*, "A Role for Cyclosporin A in Gene Replacement Therapy," *American Journal of Human Genetics* 45:A109, 1989.

Bennett *et al.*, "Suppression of Immunological Response Against a Novel Gene Product Delivered by Implants of Genetically Modified Fibroblasts," *Molecular Biology and Medicine*, 7:471-477, 1990.

Boggs, "Targeted Gene Modification for Gene Therapy of Stem Cells," *International Journal of Cell Cloning* 8:80-96, 1990.

Brash *et al.*, "Strontium Phosphate Transfection of Human Cells in Primary Culture: Stable Expression of the Simian Virus 40 Large-T-Antigen Gene in Primary Human Bronchial Epithelial Cells," *Molecular and Cellular Biology* 7(5):2031-2034, 1987.

Brenner *et al.*, "Expression of Collagen Genes in the Liver," *Molecular Biology and Medicine* 7:105-115, 1990.

Brigham *et al.*, "Expression of a Prokaryotic Gene in Cultured Lung Endothelial Cells after Lipofection with a Plasmid Vector," *Am. Journal of Respiratory Cell. and Molecular Biology* 1:95-100, 1989.

Burrin *et al.*, "Regulation of Transfected Glycoprotein Hormone  $\alpha$ -Gene Expression in Primary Pituitary Cell Cultures," *Molecular Endocrinology* 3(10):1643-1651, 1989.

Camerini-Otero, "Right on Target," *The New Biologist* 2:337-341, 1990.

Cann *et al.*, "High Efficiency Transfection of Primary Human Lymphocytes and Studies of Gene Expression," *Oncogene* 3:123-128, 1988.

Capecchi, "High Efficiency Transformation By Direct Microinjection of DNA Into Cultured Mammalian Cells," *Cell* 22:479-488, 1980.

Capecchi, "The New Mouse Genetics: Altering the Genome by Gene Targeting," *Trends in Genetics* 5:70-76, 1989.

Capecchi, "Altering the Genome by Homologous Recombination," *Science* 244:1288-1292, 1989.

- Chang *et al.*, "High Efficiency Gene Transfection by Electroporation Using a Radio-Frequency Electric Field," *Biochimica et Biophysica Acta*, 1092:153-160, 1991.
- Chang *et al.*, "Autologous Fibroblast Implantation Feasibility and Potential Problems in Gene Replacement Therapy," *Molecular Biology and Medicine*, 7:461-470, 1990.
- Cline, "Perspectives for Gene Therapy: Inserting New Genetic Information into Mammalian Cells by Physical Techniques and Viral Vectors," *Pharmacology and Therapy* 29:69-92, 1985.
- Corey *et al.*, "Erythropoiesis in Murine Long-Term Marrow Cultures Following Transfer of the Erythropoietin cDNA into Marrow Stromal Cells," *Experimental Hematology*, 18(3):201-204, 1990.
- Crystal, "Transfer of Genes to Humans: Early Lessons and Obstacles to Success," *Science* 270:404-410, 1995.
- Daubas *et al.*, "Functional Activity of the Two Promoters of the Myosin Alkali Light Chain Gene in Primary Muscle Cell Cultures: Comparison with Other Muscle Gene Promoters and Other Culture Systems," *Nucleic Acids Research* 16(4):1251-1271, 1988.
- Dhawan *et al.*, "Systemic Delivery of Human Growth Hormone by Injection of Genetically Engineered Myoblasts," *Science* 254:1509-1512, 1991.
- Diatloff-Zito *et al.*, "Abnormal Response to DNA Crosslinking Agents of Fanconi Anemia Fibroblasts can be Corrected by Transfection with Normal Human DNA," *Proceedings of the National Academy of Sciences U.S.A.* 83:7034-7038, 1986.
- Doering *et al.*, "Expression of a Novel Gene Product by Transplants of Genetically Modified Primary Fibroblasts in the Central Nervous Systems," *Journal of Neuroscience Research* 29:292-298, 1991.
- Doetschman *et al.*, "Targeted Correction of a Mutant HPRT Gene in Mouse Embryonic Stem Cells," *Nature*, 330:576-578, 1987.
- Doetschman *et al.*, "Targeted Mutation of the *HPRT* Gene in Mouse Embryonic Stem Cells," *Proceedings of the National Academy of Sciences U.S.A.* 85:8583-8587, 1988.
- Drucker, *et al.*, "Cell-Specific Post-Translational Processing of Preproglucagon Expressed from a Metallothionein-Glucagon Fusion Gene," *The Journal of Biological Chemistry* 261(21):9637-9643, 1986.
- Duncan *et al.*, *Biochemistry (Moscow)* 62:1263-1274, 1997.
- Finn *et al.*, "Homologous Plasmid Recombination is Elevated in Immortally Transformed Cells," *Molecular and Cellular Biology*, 9:4009-4017, 1989.
- Fishel *et al.*, "Biochemical Studies of Homologous and Nonhomologous Recombination in Human Cells," *Biochimie*, 73:257-267, 1991.
- Fountain *et al.*, "Transfection of Primary Human Skin Fibroblasts by Electroporation," *Gene* 68(1):167-172, 1988.
- Friedmann, "Progress Toward Human Gene Therapy," *Science* 244:1275-1281, 1989.
- Frohman, "Cut, Paste, and Save: New Approaches to Altering Specific Gene in Mice," *Cell* 56:145-147, 1989.
- Gao *et al.*, "A Novel Cationic Liposome Reagent for Efficient Transfection of Mammalian Cells," *Biochemical and Biophysical Research Communications* 179(1):280-285, 1995.

Gareis *et al.*, "Homologous Recombination of Exogenous DNA Fragments with Genomic DNA in Somatic Cells of Mice," *Cellular and Molecular Biology* 37(2):191-203, 1991.

Ginot *et al.*, "Transfection of Hepatic Genes Into Adult Rat Hepatocytes in Primary Culture and Their Tissue-Specific Expression," *European Journal of Biochemistry* 180:289-294, 1989.

Glover, "Expression of Cloned Genes in Animal Cells," In "Gene Cloning, The Mechanics of DNA Manipulation," pp. 179-202, Chapman and Hall, New York, 1984.

Hammer *et al.*, "Partial Correction of Murine Hereditary Growth Disorder by Germ-Line Incorporation of a New Gene," *Nature* 311:65-67, 1984.

Harper *et al.*, "Expression of Transfected DNA by Primary Murine Keratinocytes," *Journal of Investigative Dermatology* 91(2):150-153, 1988.

Heartlein *et al.*, "Long-Term Production and Delivery of Human Growth Hormone," *Proceedings of the National Academy of Sciences U.S.A.* 91:10967-10971, 1994.

Hesse *et al.*, "Regulated Gene Expression in Transfected Primary Chicken Erythrocytes," *Proceedings of the National Academy of Sciences U.S.A.* 83:4312-4316, 1986.

Iannuzzi *et al.*, "The Introduction of Biologically Active Foreign Genes into Human Respiratory Epithelial Cells Using Electroporation," *Am. Rev. of Resp. Dis.* 138:965-968, 1988.

Imagawa *et al.*, "Regulatory Elements of the Erythropoietin Gene," *Blood* 77(2):278-285, 1991.

Itzhaki *et al.*, "Targeted Disruption of a Human Interferon-Inducible Gene Detected by Secretion of Human Growth Hormone," *Nucleic Acids Research* 19(4):3835-3842, 1991.

Jensen *et al.*, "High-Frequency Transfection of Cultured Human Epidermal Basal Cells That Differentiate to Form a Multilayered Tissue," *Experimental Cell Research* 189:163-168, 1990.

Joyner *et al.*, "Production of a mutation in mouse En-2 gene by homologous recombination in embryonic stem cells," *Nature* 338:153-155, 1989.

Kaufman *et al.*, "Strategies for Obtaining High Level Expression in Mammalian Cells," *Technique* 2:221-236, 1990.

Keating *et al.*, "Gene Transfer by Electroporation: A Model for Gene Therapy," *Progress in Clinical Biological Research* 333:491-498, 1990.

Keating *et al.*, "Effect of Different Promoters on Expression of Genes Introduced Into Hematopoietic and Marrow Stromal Cells by Electroporation," *Experimental Hematology* 18:99-102, 1990.

Kendrew, *The Encyclopedia of Molecular Biology*, Blackwell Science Ltd., Oxford, p. 1085, 1994.

Kramerova *et al.*, "Expression of the Cloned Human Erythropoietin Gene in CHO Cells," *Biopolim Kletka* 5(2):47-51, 1989.

Kremer *et al.*, "Regulation of Parathyroid Hormone-like Peptide in Cultured Normal Human Keratinocytes," *The Journal of Clinical Investigation* 87:884-893, 1991.

- Kreymann *et al.*, "Glucagon-Like Peptide-1 7-36: A Physiological Incretin In Man," *The Lancet* 2:1300-1304, 1987.
- Kriegler, "Gene Transfer and Expression: A Laboratory Manual," Stockton Press, New York, 1990.
- Le Mouellic *et al.*, "Targeted Replacement of the Homeobox Gene *Hox-3.1* by the *Escherichia coli lacZ* in Mouse Chimeric Embryos," *Proceedings of the National Academy of Sciences U.S.A.* 87:4712-4716, 1990.
- Ledley, "Clinical Considerations in the Design of Protocols for Somatic Gene Therapy," *Human Gene Therapy* 2:77-83, 1991.
- Lee *et al.*, "Glucagon Gene 3'-Flanking Sequences Direct Formation of Proglucagon Messenger RNA 3'-Ends in Islet and Nonislet Cells Lines," *Molecular Endocrinology*, 4(6):800-806, 1990.
- Lewin, *Genes IV*, Oxford University Press, Oxford, p. 820, 1990.
- Litwer *et al.*, "Reversion of the Maple Syrup Urine Disease Phenotype of Impaired Branched Chain Alpha-Ketoacid Dehydrogenase Complex Activity in Fibroblasts from an Affected Child," *The Journal of Biological Chemistry* 264:14597-14600, 1989.
- Loeffler *et al.*, "Lipopolyamine-Mediated Transfection Allows Gene Expression Studies in Primary Neuronal Cells," *Journal of Neurochemistry* 54:1812-1815, 1990.
- Lu *et al.*, "Gene Transfer by Lipofection in Rabbit and Human Secretory Epithelial Cells," *Pflügers Archives* 415:198-203, 1989.
- Lupton *et al.*, "Dominant Positive and Negative Selection Using A Hygromycin Phosphotransferase-Thymidine Kinase Fusion Gene," *Molecular and Cellular Biology* 11(6):3374-3378, 1991.
- Mansour, "Gene Targeting in Murine Embryonic Stem Cells: Introduction of Specific Alterations into the Mammalian Genome," *Genet. Anal. Tech Appl.* 7:219-227, 1990.
- Mansour *et al.*, "Disruption of the Proto-Oncogene *int-2* in Mouse Embryo-Derived Stem Cells: A General Strategy for Targeting Mutations to Non-Selectable Genes," *Nature* 336:348-352, 1988.
- Marshall, "Gene Therapy's Growing Pains," *Science* 269:1050-1055, 1995.
- Mercola *et al.*, "Insertion of New Genetic Information into Bone Marrow Cells of Mice: Comparison of Two Selectable Genes," *Annals New York Academy of Sciences*, p. 272-280, 1982.
- Mes-Masson *et al.*, "Expression of Oncomodulin Does Not Lead to the Transformation or Immortalization of Mammalian Cells *In Vitro*," *Journal of Cellular Science*, 94:517-25, 1989.
- Morgan *et al.*, "Expression of an Exogenous Growth Hormone Gene by Transplantable Human Epidermal Cells," *Science* 237:1476-1479, 1987.
- Morgenstern *et al.*, "Advanced Mammalian Gene Transfer: High Titre Retroviral Vectors With Multiple Drug Selection Markers and a Complementary Helper-Free Packaging Cell Line," *Nucleic Acids Research* 18(12):3587-3596, 1990.
- Narayanan *et al.*, "*In Vivo* Expression of a Nonselected Gene Transferred into Murine Hematopoietic Stem Cells by Electroporation," *Biochemical and Biophysical Research Communications* 141:1018-1024, 1986.

- Ogura *et al.*, "Implantation of Genetically Manipulated Fibroblasts into Mice as Antitumor  $\alpha$ -Interferon Therapy," *Cancer Research* 50:5102-5106, 1990.
- Orkin *et al.*, "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy," 1995.
- Palmer *et al.*, "Genetically Modified Skin Fibroblasts Persist Long After Transplantation But Gradually Inactivate Introduced Genes," *Proceedings of the National Academy of Sciences U.S.A.* 88:1330-1334, 1991.
- Palmiter *et al.*, "Metallothionein-Human GH Fusion Genes Stimulate Growth of Mice," *Science* 222:809-814, 1983.
- Pasco *et al.*, "Laboratory Methods, Efficient DNA-Mediated Gene Transfer into Primary Cultures of Adult Rat Hepatocytes," *DNA* 8(7):535-541, 1989.
- Ponder *et al.*, "Evaluation of Relative Promoter Strength in Primary Hepatocytes Using Optimized Lipofection," *Human Gene Therapy* 2:41-52, 1991.
- Ponticelli *et al.*, "Correction of Anaemia with Recombinant Human Erythropoietin," *Nephron* 52:201-208, 1989.
- Potter, "Electroporation in Biology: Methods, Applications, and Instrumentation," *Analytical Biochemistry* 174:361-73, 1988.
- Powell, "Human Erythropoietin Gene: High Level Expression In Stably Transfected Mammalian Cells and Chromosome Localization," *Proceedings of the National Academy of Sciences U.S.A.* 83:6465-6469, 1986.
- Rippe *et al.*, "DNA-Mediated Gene Transfer Into Adult Rat Hepatocytes in Primary Culture," *Molecular and Cellular Biology* 10(2):689-695, 1990.
- Robertson, "Using Embryonic Stem Cells to Introduce Mutations into the Mouse Germ Line," *Biology of Reproduction* 44:238-245, 1991.
- Rodriguez *et al.*, "Recombinant DNA Techniques: An Introduction," The Benjamin/Cummings Publishing Company, Inc., London, 1983.
- Rosenfeld *et al.*, "*In Vivo* Transfer of the Human Cystic Fibrosis Transmembrane Conductance Regulator Gene to the Airway Epithelium," *Cell* 68:143-155, 1992.
- Sambrook *et al.*, "Molecular Cloning," Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, p. 16.3-16.4, 1989.
- Sandhu *et al.*, "Human Gene Therapy," *Critical Reviews in Biotechnology* 17:307-326, 1997.
- Scharfmann *et al.*, "Long-Term *In Vivo* Expression of Retrovirus-Mediated Gene Transfer in Mouse Fibroblast Implants," *Proceedings of the National Academy of Sciences U.S.A.* 88:4626-4630, 1991.
- Sedivy *et al.*, "Positive Genetic Selection for Gene Disruption in Mammalian Cells by Homologous Recombination," *Proceedings of the National Academy of Sciences U.S.A.* 86:227-231, 1989.
- Selden *et al.*, "Regulation of Insulin-Gene Expression," *The New England Journal of Medicine* 317:1067-1076, 1987.
- Selden *et al.*, "Implantation of Genetically Engineered Fibroblasts into Mice: Implications for Gene Therapy," *Science* 236:714-718, 1987.



- Shesely *et al.*, "Correction of a Human  $\beta^s$ -globin Gene by Gene Targeting," *Proceedings of the National Academy of Sciences U.S.A.* 88:4294-4298, 1991.
- Sittler *et al.*, "Tissue-Specific Expression of the Rat Growth Hormone Gene is Due to the Interaction of Multiple Promoter, Not Enhancer, Elements," *DNA and Cell Biology* 9(7):511-518, 1990.
- Smith, "Regulation of Hematopoiesis," *The Yale Journal of Biology and Medicine*, 63(5):371-80, 1990.
- Spandidos, "Electric Field-Mediated Gene Transfer (Electroporation) into Mouse Friend and Human K562 Erythroleukemic Cells," *Gene Anal. Tech.*, 4:50-56, 1987.
- Stacey *et al.*, "Electroporation and DNA-Dependent Cell Death in Murine Macrophages," *Immunology and Cell Biology* 71:75-85, 1993.
- St. Louis *et al.*, "An Alternative Approach to Somatic Cell Gene Therapy," *Proceedings of the National Academy of Sciences U.S.A.*, 85:3150-3154, 1988.
- Tatsuka *et al.*, "An Improved Method of Electroporation for Introducing Biologically Active Foreign Genes Into Cultured Mammalian Cells," *Experimental Cell Research* 178:154-162, 1988.
- Thomas *et al.*, "Site-Directed Mutagenesis by Gene Targeting in Mouse Embryo-Derived Stem Cells," *Cell* 51:503-512, 1987.
- Thomas *et al.*, "Targeted Disruption of the Murine int-1 Proto-oncogene Resulting in Severe Abnormalities in Midbrain and Cerebellar Development," *Nature* 346:847-850, 1990.
- Thompson *et al.*, "Germ Line Transmission and Expression of a Corrected HPRT Gene Produced by Gene Targeting in Embryonic Stem Cells," *Cell* 56:313-321, 1989.
- Toneguzzo *et al.*, "Stable Expression of Selectable Genes Introduced into Human Hematopoietic Stem Cells by Electric Field-Mediated DNA Transfer," *Proceedings of the National Academy of Sciences U.S.A.* 83:3496-3499, 1986.
- Treco *et al.*, "Non-Viral Gene Therapy," *Molecular Medicine Today* 1:314-321, 1995.
- Treco *et al.*, "Fibroblast Cell Biology and Gene Therapy," *Somatic Gene Therapy*, ISBN 0-8493-2440-8:49-60, 1995.
- Tur-Kaspa *et al.*, "Use of Electroporation to Introduce Biologically Active Foreign Genes Into Primary Rat Hepatocytes," *Molecular and Cellular Biology* 6:716-718, 1986.
- Vega, "Prospects for Homologous Recombination in Human Gene Therapy," *Human Genetics* 87:245-253, 1991.
- Verma, "Gene Therapy," *Scientific American*, 68-84, November, 1990.
- Vogelstein *et al.*, "The Multistep Nature of Cancer," *Trends in Genetics* 9(4):138-141, 1993.
- Weatherall, "Scope and Limitations of Gene Therapy," *British Medical Bulletin* 51:1-11, 1995.
- Weidle *et al.*, "A New Expression System for Mammalian Cells Based on Putative Replicator Sequences of the Mouse and a Truncated Thymidine Kinase Gene," *Gene* 73:427-437, 1988.

Werner *et al.*, "Expression of Transfected Genes by Differentiated, Postmitotic Neurons and Photoreceptors in Primary Cell Cultures," The Journal of Neuroscience Research 25:50-57, 1990.

Wolff *et al.*, "Direct Gene Transfer Into Mouse Muscle *In Vivo*," Science 247:1465-1468, 1990.

Wu, "Receptor-Mediated Gene Delivery *In Vivo*," The Journal of Biological Chemistry 266(22):14338-14342, 1991.

Yang *et al.*, "*In Vivo* and *In Vitro* Gene Transfer to Mammalian Somatic Cells by Particle Bombardment," Proceedings of the National Academy of Sciences U.S.A. 87:9568-9572, 1990.

Zheng *et al.*, "Primary cells and established cell lines join DNA ends with the same efficiency relative to homologous recombination," Plasmid 22:99-105, 1989.

Zheng *et al.*, "Fidelity of Targeted Recombination in Human Fibroblasts and Murine Embryonic Stem Cells," Proceedings of the National Academy of Sciences 88:8067-8071, 1991.

This statement is being filed before the receipt of a first Office Action on the merits.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: September 8, 2000

Susan M. Michaud  
Susan M. Michaud, Ph.D.  
Reg. No. 42,885

Clark & Elbing LLP  
176 Federal Street  
Boston, MA 02110  
Telephone: 617-428-0200  
Facsimile: 617-428-7045

\\Ntserver\documents\50010\50010.006006 Information Disclosure Statement.wpd